FACULTY OF SEXUAL & REPRODUCTIVE HEALTHCARE

ROYAL COLLEGE OF OBSTETRICIANS & GYNAECOLOGISTS

Faculty of Sexual & Reproductive Healthcare Clinical Guidance



Problematic Bleeding with Hormonal Contraception

Clinical Effectiveness Unit

July 2015

ISSN 1755-103X

Document reference number	04/FSRH/Problematic Bleeding/2015
Title	Problematic Bleeding with Hormonal Contraception
Author/publisher	Faculty of Sexual & Reproductive Healthcare (FSRH)
Publication date	July 2015
Description/descriptors	Irregular bleeding, bleeding, breakthrough bleeding, spotting
Cross references	*United Kingdom Medical Eligibility Criteria (UKMEC) 2009*
Superseded documents	*Management of Unscheduled Bleeding in Women Using Hormonal Contraception 2009*
Update/amendment level	Partial amendment – no changes to recommendations and practice
Review date	July 2020

GRADING OF RECOMMENDATIONS

A Evidence based on randomised controlled trials

B Evidence based on other robust experimental or observational studies

C Evidence is limited but the advice relies on expert opinion and has the endorsement of respected authorities

✓ Good Practice Point where no evidence exists but where best practice is based on the clinical experience of the guideline group

Published by the Faculty of Sexual & Reproductive Healthcare
Registered in England No. 2804213 and Registered Charity No. 1019969

First published in 2015

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ABBREVIATIONS USED

CEU	Clinical Effectiveness Unit
CHC	combined hormonal contraception/contraceptive
CI	confidence interval
COC	combined oral contraception/contraceptive
CVR	combined vaginal ring
DMPA	depot medroxyprogesterone acetate
DSG	desogestrel
EE	ethinylestradiol
FSRH	Faculty of Sexual & Reproductive Healthcare
HMB	heavy menstrual bleeding
IM	intramuscular
IUS	intrauterine system
LNG	levonorgestrel
LNG-IUS	levonorgestrel-releasing intrauterine system
NHSCSP	National Health Service Cervical Screening Programme
NICE	National Institute for Health and Care Excellence
NSAID	non-steroidal anti-inflammatory drug
POP	progestogen-only pill
RCT	randomised controlled trial
RR	relative risk
SC	subcutaneous
STI	sexually transmitted infection
UKMEC	United Kingdom Medical Eligibility Criteria
WHO	World Health Organization
WHOSPR	World Health Organization *Selected Practice Recommendations for Contraceptive Use*

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SUMMARY OF KEY RECOMMENDATIONS

✓ Before starting hormonal contraception, women should be advised about the bleeding patterns expected both initially and in the longer term.

C A clinical history should be taken from women using hormonal contraception who have problematic bleeding to identify the possibility of an underlying cause.

✓ Hormonal contraception users with problematic bleeding who are at risk of sexually transmitted infections (STIs) should be tested for *Chlamydia trachomatis* as a minimum. Testing for *Neisseria gonorrhoea* will depend on sexual risk, local prevalence and availability of dual testing.

✓ Women using hormonal contraception who have problematic bleeding and are eligible for, but not participating in, a National Health Service Cervical Screening Programme (NHSCSP) should have a cervical screen.

✓ A pregnancy test is indicated for sexually active women using hormonal contraception with problematic bleeding.

✓ An examination may not be required in women attending with problematic bleeding who are using hormonal contraception, if after taking a clinical history there are no risk factors for STIs, no concurrent symptoms suggestive of underlying causes, they are participating in an NHSCSP, and have had no more than 3 months of problematic bleeding.

✓ A speculum examination should be performed for women using hormonal contraception who have problematic bleeding if they have persistent bleeding or a change in bleeding after at least 3 months of use, if medical treatment has failed or if they have not participated in an NHSCSP.

✓ An endometrial biopsy should be considered in women aged ≥45 years or in women aged <45 years with risk factors for endometrial cancer who have persistent problematic bleeding after the first 3 months of use of a method or who present with a change in bleeding pattern.

✓ The role of endometrial polyps, fibroids or ovarian cysts as a cause of problematic bleeding is uncertain. Nevertheless, for all women using hormonal contraception who have problematic bleeding, if such a structural abnormality is suspected a transvaginal ultrasound scan and/or hysteroscopy may be indicated.

✓ It is not generally recommended that a combined oral contraceptive pill (COC) be changed within the first 3 months of use as bleeding disturbances often settle in this time.

✓ For women using a COC the lowest dose of ethinylestradiol (EE) to provide good cycle control should be used. However, the dose of EE can be increased to a maximum of 35 µg to provide good cycle control.

✓ Bleeding is common in the initial months of progestogen-only method use and may settle without treatment. If treatment encourages a woman to continue with the method it may be considered.

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✓ There is no evidence that changing the type and dose of progestogen-only pill (POP) will improve problematic bleeding; bleeding patterns may vary with different POP preparations and this may help some individuals.

B For women using a progestogen-only injectable contraceptive who have problematic bleeding, mefenamic acid 500 mg twice daily (or as licensed up to three times daily) for 5 days can reduce the length of a bleeding episode but has little effect on bleeding in the longer term.

C For women with problematic bleeding using a progestogen-only injectable, implant or intrauterine system (IUS) who wish to continue with the method and are medically eligible, a COC may be tried for 3 months (this can be used in the usual cyclic manner or continuously without a pill-free interval and is outside the product licence).

✓ Longer-term use of COC has not been studied in relation to the progestogen-only injectable, implant or IUS methods. If bleeding recurs following 3 months use of COC, longer-term use is a matter of clinical judgement.

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A unit funded by the FSRH and supported by NHS Greater Glasgow & Clyde/ NHS Lothian to provide guidance on evidence-based practice

FSRH Guidance (July 2015)

Problematic Bleeding with Hormonal Contraception

(Revision due by July 2020)

1 Purpose and Scope

This guidance brings together evidence and expert opinion on the management of problematic bleeding in women using hormonal contraception [i.e. the combined oral contraceptive pill (COC), transdermal patch, combined vaginal ring (CVR), progestogen-only pill (POP), progestogen-only injectable, progestogen-only implant or intrauterine system (IUS)]. The term problematic bleeding in this guidance refers to breakthrough bleeding, spotting, prolonged or frequent bleeding (Box 1).[1] This document supersedes previous Faculty of Sexual & Reproductive Healthcare (FSRH) guidance on the management of unscheduled bleeding.[2] The main changes from the previous guidance are:

- Information on the CVR
- Information on Sayana Press®, a subcutaneous progestogen-only injectable
- Information on Jaydess®, a 13.5 mg levonorgestrel IUS (LNG-IUS)
- Information on estradiol-containing COC.

The management of women who present with problematic bleeding while using hormonal contraception is challenging. For many women problematic bleeding will be due to the contraceptive method itself: the pattern and duration of bleeding and the likelihood of this settling will vary with the method used (Table 1). Women may consider that the contraceptive and non-contraceptive benefits of a method outweigh the inconvenience of unpredictable bleeding. After reassurance that there is no serious underlying cause, they may be happy to continue using the method.

The management of women with problematic bleeding in the 3–6 months after starting a new method of hormonal contraception may differ from that of women who continue to have problematic bleeding in the longer term or who present with a change in bleeding pattern. A clinical history (Box 2) should highlight possible underlying causes and provide a guide to the most appropriate examination, investigation and treatment options required. Reassuringly, in community populations, endometrial cancer is very rare in women of reproductive age who

Box 1 Clinically important bleeding patterns in women aged 15–44 years[1]

Scheduled bleeding	Menstruation or regular withdrawal bleeding with combined hormonal contraception (CHC)
Other bleeding patterns	
Frequent bleeding	More than five bleeding episodes[a] within a reference period[b]
Infrequent bleeding	Fewer than three bleeding episodes[a] within a reference period[b]
Prolonged bleeding	Bleeding episode[a] lasting 14 days or more
Spotting	Vaginal discharge containing blood, that may not require the use of sanitary protection
Breakthrough bleeding	Unscheduled bleeding in women using CHC
Amenorrhoea	No bleeding or spotting days throughout the 90-day reference period[b]

[a]Bleeding episode: one or more consecutive days of bleeding, bounded by bleed-free days.
[b]Reference period: a 90-day period of time during use of a hormonal contraceptive method.

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are using hormonal contraception and who do not have risk factors for endometrial cancer (such as obesity, polycystic ovarian syndrome or diabetes). Cervical cancer is also rare in this population, especially in women who comply with National Health Service Cervical Screening Programmes (NHSCSPs).

A management plan is outlined that can be tailored to the individual woman (Figure 1). Evidence to support the management plan is provided in this guidance. It is a guide only and can be used to develop a care pathway taking account of local expertise and ease of referral/access to specialist services and investigations.

Recommendations within this document are based on the best available evidence and the consensus opinion of experts. A key to the grading of recommendations, derived from levels of evidence, is provided on the inside front cover of this document. Details of the methods used by the Clinical Effectiveness Unit (CEU) in developing this guidance are outlined in Appendix 1 and in the CEU section of the FSRH website (www.fsrh.org). The recommendations included should be used to guide clinical practice but are not intended to serve alone as a standard of medical care or to replace clinical judgement in the management of individual cases.

2 Background

During a normal menstrual cycle the endometrium is exposed to circulating sex steroids. It is the sequential exposure of the endometrium to the natural steroids, estradiol and progesterone, that leads to characteristic histological features.[3]

Estradiol exposure during the follicular phase is responsible for endometrial proliferation. Exposure to progesterone in the luteal phase results in secretory differentiation. Progesterone is anti-estrogenic and inhibits endometrial growth and glandular differentiation. It is the withdrawal of estradiol and progesterone, in the absence of pregnancy, which triggers the onset of menstrual bleeding.[4]

Exogenous administration of sex steroids, in the form of hormonal contraception, dramatically influences endometrial histology.[4,5]

The exact mechanisms of problematic bleeding associated with hormonal contraception are largely unexplained. The evidence to date implicates superficial blood vessel fragility within the endometrium and local changes in endometrial steroid response, structural integrity, tissue perfusion and local angiogenic factors as contributing factors.[5] Since there are no established long-term interventions available to manage problematic bleeding, a greater understanding of the mechanisms involved is required.

3 Expected Bleeding Patterns Associated with Hormonal Contraception

Pre-method counselling about expected bleeding patterns may reduce concerns and encourage continued use of a given method of hormonal contraception.[6,7] If bleeding patterns fall outside the expected 'normal' patterns associated with different contraceptive methods at different durations of use (outlined in Table 1), examination, investigation or treatment may be indicated.

✓ Before starting hormonal contraception, women should be advised about the bleeding patterns expected both initially and in the longer term.

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Table 1 Expected bleeding patterns after commencing hormonal contraception and in the longer term

Contraceptive method	Bleeding patterns in women in the first 3 months	Bleeding patterns in women in the longer term
Combined hormonal contraception (pill, patch or ring)	Up to 20% of COC users have irregular bleeding	Irregular bleeding usually settles[8] No significant differences in bleeding between pill and patch use[9,10] The combined vaginal ring may afford better cycle control (less unscheduled bleeding) when compared to the pill[9] Users of estradiol COC have reported shorter, lighter bleeds and a higher rate of absent withdrawal bleeds than women using an EE-containing COC[11]
Progestogen-only pill	Bleeding is unpredictable With traditional POPs, one-third of women have a change in bleeding[12] A comparative study of DSG LNG POP reported that frequent bleeding, prolonged bleeding and infrequent bleeding were more common in DSG users than LNG users in the first reference period of 90 days[13]	Bleeding may not settle with time Traditional POP users can be advised that frequent and irregular bleeding are common, while prolonged bleeding and amenorrhoea are less likely[14] As a guide, women considering DSG-only POP can be advised that after 12 months of use, over a 3-month period approximately:[13,14] ● 5 in 10 women can expect to be amenorrhoeic or have infrequent bleeding ● 4 in 10 women can expect to have 3–5 bleeding spotting/episodes (regular) ● 1 in 10 women can expect ≥6 bleeding/spotting episodes (frequent bleeding) ● 2 in 10 women will experience bleeding/spotting episodes lasting for more than 14 days (prolonged bleeding)
Progestogen-only injectable (IM and SC)	Bleeding disturbances (spotting, light, heavy or prolonged bleeding) are common.[15–18] Around 1 in 10 women may be amenorrhoeic in the first 3 months of use[16]	Rates of amenorrhoea increase with duration of use and are similar for IM and SC DMPA. Around 50% or more are amenorrhoeic at 12 months[16,18,19]
Progestogen-only implant	Bleeding disturbances are common. The bleeding pattern in the first 3 months is broadly predictive of future bleeding patterns for many women[20,21]	As a guide, around: ● 2 in 10 women are amenorrhoeic ● 3 in 10 women have infrequent bleeding ● Fewer than 1 in 10 women have frequent bleeding ● 2 in 10 women have prolonged bleeding[20,21] In 75% of reference periods bleeding-spotting days are fewer than or comparable to those observed during the natural cycle, but they occur at unpredictable intervals[20]
Levonorgestrel-releasing intrauterine system (LNG-IUS) 52 mg (Mirena®)	Frequent bleeding/spotting is common in the first few months after insertion[22]	There is a decrease over time in the number of bleeding and spotting days with all doses of LNG-IUS[22] A 90% reduction in menstrual blood loss has been demonstrated over 12 months of 52 mg LNG-IUS use[23] At 1 year, infrequent bleeding is usual with the LNG-IUS and some women will be amenorrhoeic[24]. 24% of 52 mg LNG-IUS users are amenorrhoeic at 3 years[22]
LNG-IUS 13.5 mg (Jaydess®)	Frequent bleeding/spotting is common in the first few months after insertion[22]	There is a decrease over time in the number of bleeding and spotting days with all doses of LNG-IUS[22] Users of the 13.5 mg LNG-IUS report more spotting days than bleeding days over the duration of licensed use[22] Fewer women (13% at 3 years) will experience amenorrhoea with this dose of LNG-IUS compared to the 52 mg LNG-IUS[22]

CHC, combined hormonal contraception; COC, combined oral contraceptive pill; DMPA, depot medroxyprogesterone acetate; DSG, desogestrel; EE, ethinylestradiol; IM, intramuscular; LNG, levonorgestrel; LNG-IUS, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill; SC, subcutaneous.

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4 Medical Eligibility for Contraceptive Use in Women with Abnormal Bleeding

The United Kingdom Medical Eligibility Criteria for Contraceptive Use (UKMEC)[25] provides recommendations for the safe use of contraception and includes categories for the use of hormonal contraception by women with irregular, heavy or prolonged vaginal bleeding.

5 Management of Women with Problematic Bleeding

An individual approach should be taken when considering the management of women using hormonal contraception who present with problematic bleeding. The decision to examine, investigate and/or treat will depend on clinical assessment (Box 2).

The health professional making an assessment of women using hormonal contraception with problematic bleeding should:

- Take a clinical history
- Exclude sexually transmitted infections (STIs)
- Check cervical screening history
- Consider the need for a pregnancy test
- Exclude underlying pathology.

5.1 Clinical history

A clinical history should be taken to identify or exclude some of the possible underlying causes of problematic bleeding in women using hormonal contraception (Box 2).

5.2 Sexually transmitted infections

All women using hormonal contraception who have problematic bleeding should be assessed to identify the risk of STIs. *Chlamydia trachomatis* is the most prevalent bacterial STI in the UK and although up to 70% of women with *C. trachomatis* are asymptomatic, abnormal bleeding may be a presenting symptom.[26–28] Risk factors for STIs include age <25 years, a new sexual partner, or more than one partner in the last year.[26–28] If deemed at risk for an STI, *C. trachomatis* should be excluded as a minimum. A single vaginal swab can be sent for combined *C. trachomatis* and *Neisseria gonorrhoea* testing by nucleic acid amplification testing.[28] Vaginal swabs can be self-taken if preferred. Urine testing is no longer recommended for STI screening in women.[28]

Box 2 Points to cover in the clinical history from a woman using hormonal contraception who presents with problematic bleeding

Clinical history taking should include an assessment of a woman's:

- Own concerns
- Current method of contraception and duration of use[a]
- Compliance with the current contraceptive method[b]
- Use of any medications (including over-the-counter preparations) which may interact with the contraceptive method
- Illness/condition that may affect absorption of orally administered hormones
- Cervical screening history[c]
- Risk of sexually transmitted infections (i.e. those aged <25 years, or at any age with a new partner, or more than one partner in the last year)
- Bleeding pattern before starting hormonal contraception, since starting and currently
- Other symptoms suggestive of an underlying cause (e.g. abdominal or pelvic pain, postcoital bleeding, dyspareunia, heavy menstrual bleeding)
- Possibility of pregnancy

[a]Progestogen-only methods are more likely to result in problematic bleeding than combined hormonal methods.
[b]For example, missed pills.
[c]A woman presenting with abnormal bleeding who is participating in a National Cervical Screening Programme does not require a cervical screen unless one is due.

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5.3 Cervical screening

A cervical screening test is not a diagnostic test for cancer. Cervical screening history should be checked to ensure that women are participating in an NHSCSP. This may have been checked when hormonal contraception was initiated but should be reviewed if a woman presents with problematic bleeding. A cervical screen can be taken if it is due or overdue. No evidence was identified in the scientific literature to support cervical screening if not due.[29–31]

5.4 Pregnancy test

A pregnancy test should be undertaken in sexually active women with problematic bleeding using hormonal contraception. However, no evidence was identified which suggested that problematic bleeding in a woman who has been using hormonal methods consistently and correctly is associated with an increased risk of pregnancy.

C A clinical history should be taken from women using hormonal contraception who have problematic bleeding to identify the possibility of an underlying cause.

✓ Hormonal contraception users with problematic bleeding who are at risk of STIs should be tested for *C. trachomatis* as a minimum. Testing for *N. gonorrhoea* will depend on sexual risk, local prevalence and availability of dual testing.

✓ Women using hormonal contraception who have problematic bleeding and are eligible for, but not participating in, an NHSCSP should have a cervical screen.

✓ A pregnancy test is indicated for sexually active women using hormonal contraception who have problematic bleeding.

5.5 Clinical examination

5.5.1 When examination may not be required

Problematic bleeding in the first 3 months after starting a new hormonal contraceptive method is common and likely to improve (Table 1). A gynaecological examination is not required if, after taking a clinical history, there are no risk factors for STIs, no concurrent symptoms suggestive of underlying causes, and the woman is participating in an NHSCSP (Figure 1). Some women may be happy to continue with the method after this initial assessment but follow-up should be offered in the event of persistent bleeding, other symptoms or concerns.

✓ An examination may not be required in women attending with problematic bleeding, who are using hormonal contraception, if after taking a clinical history there are no risk factors for STIs, no concurrent symptoms suggestive of underlying causes, they are participating in an NHSCSP and have had no more than 3 months of problematic bleeding.

5.5.2 When is examination required?

An examination is warranted to visualise the cervix by speculum examination (Figure 1):

- For persistent bleeding beyond the first 3 months of use
- For new symptoms or a change in bleeding after at least 3 months of use
- If a woman has not participated in an NHSCSP
- If requested by a woman
- After a failed trial of the limited medical management available (Figure 2)
- If there are other symptoms such as pain, dyspareunia, or postcoital bleeding. [NB. These symptoms would also warrant bimanual examination.]

The 3-month cut-off is given as a guide only because some methods, in particular the LNG-IUS or progestogen-only implant, may commonly cause bleeding after the first 3 months of use. Visualisation of the cervix can identify polyps that may warrant referral for appropriate management. Most cases of cervical cancer are prevented or identified by screening at an asymptomatic stage. However, visualisation of the cervix may identify the very occasional case

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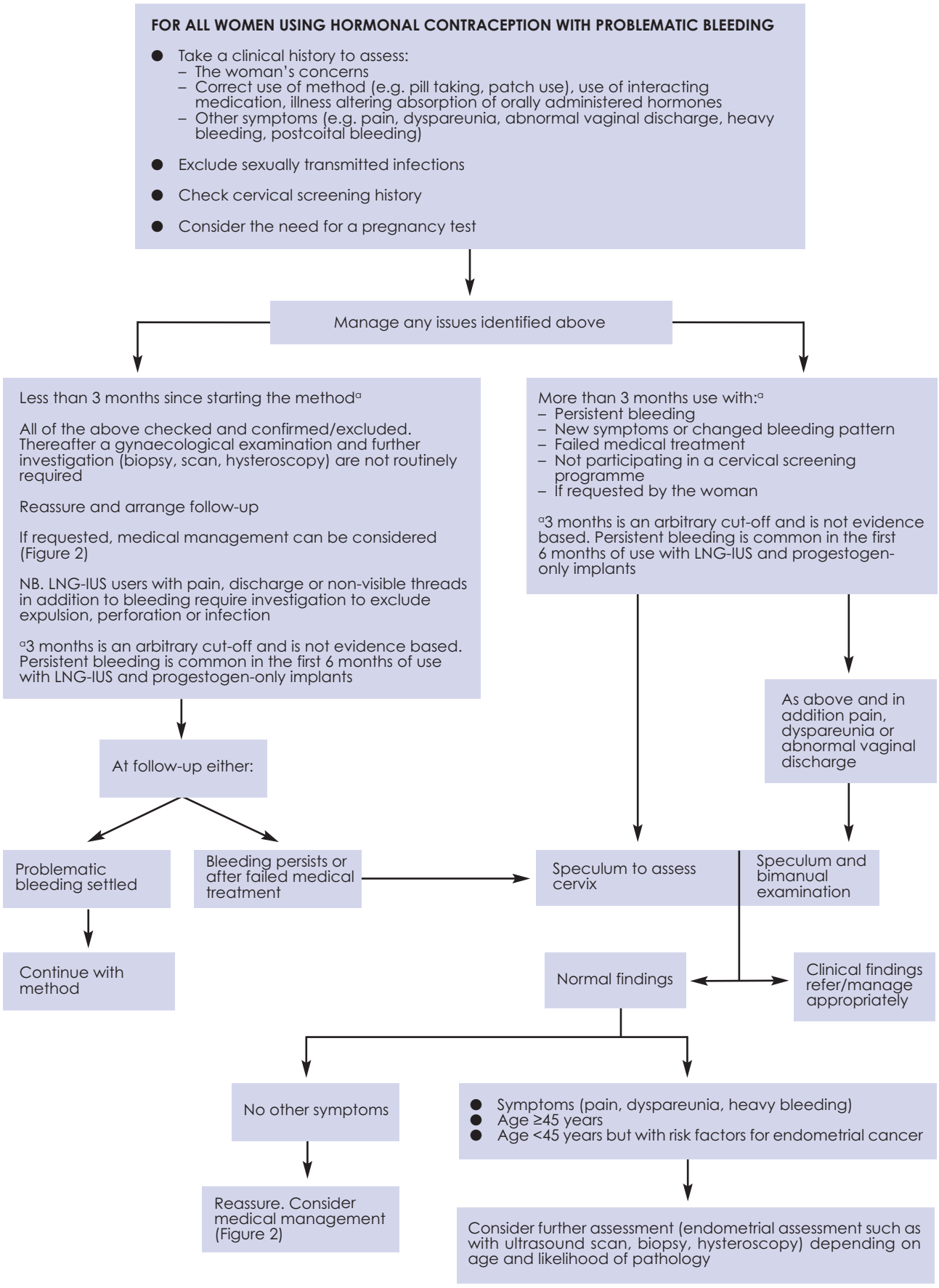

Figure 1 Example of a suggested management plan for a woman using hormonal contraception with unscheduled bleeding.

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of cervical cancer that is not detected by screening and which presents with abnormal vaginal bleeding. Pelvic examination and an urgent referral to a colposcopy clinic is required if cancer is suspected.[29,31]

Guidance from the National Institute for Health and Care Excellence (NICE) on the management of heavy menstrual bleeding (HMB)[32] recommends a speculum and bimanual examination if there are additional symptoms such as intermenstrual or postcoital bleeding, pelvic pain or pressure symptoms suggestive of a structural or histological abnormality. This advice is also appropriate for women with problematic bleeding using hormonal contraception.

✓ A speculum examination should be performed for women using hormonal contraception who have problematic bleeding if they have persistent bleeding or a change in bleeding after at least 3 months of use, if medical treatment has failed or if they have not participated in an NHSCSP.

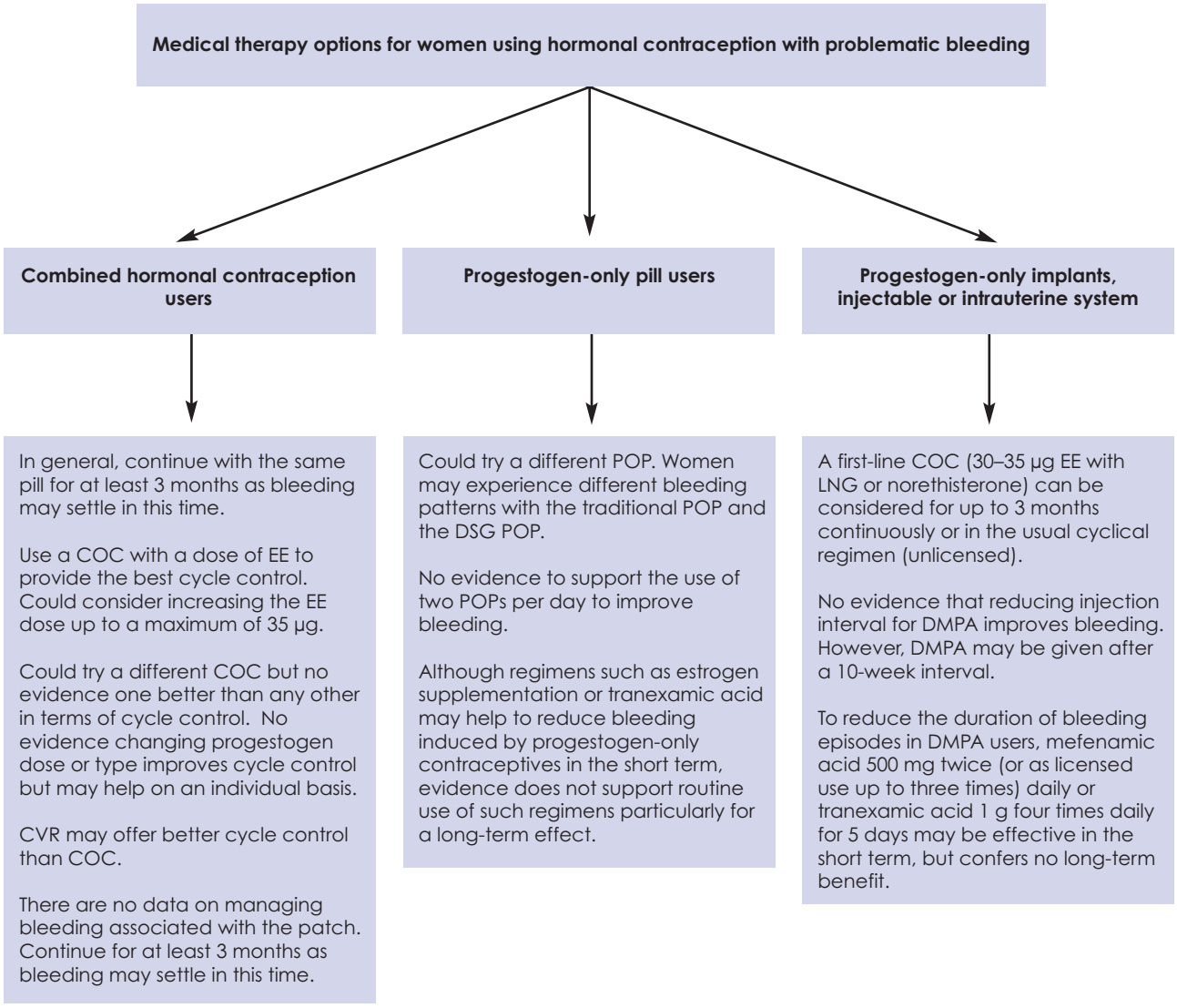

Figure 2 Medical therapy options for women using hormonal contraception with problematic bleeding. COC, combined oral contraceptive pill; CVR, combined vaginal ring; DMPA, depot medroxyprogesterone acetate; DSG, desogestrel; EE, ethinylestradiol; LNG, levonorgestrel; POP, progestogen-only pill.

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5.6 When is further investigation required?

5.6.1 Endometrial biopsy

Endometrial cancer is rare in women of reproductive age. Use of hormonal contraception reduces endometrial cancer risk[33] but is not completely protective. An endometrial biopsy is indicated in women with problematic bleeding on hormonal contraception who may be at risk of endometrial cancer.

A NICE guideline[32] recommends that for women with HMB, an endometrial biopsy should be performed if there is persistent intermenstrual bleeding and in women aged >45 years who have treatment failure. The guideline does not comment on women using hormonal contraception.

As increasing age is a known risk factor for endometrial cancer,[34] it is recommended that an endometrial biopsy should be considered in women aged ≥45 years using hormonal contraception who present with persistent problematic bleeding or a change in bleeding pattern. Endometrial biopsy may also be indicated if a woman aged <45 years has severe or persistent symptoms and/or risk factors for endometrial cancer (e.g. obesity, type 2 diabetes mellitus or polycystic ovarian syndrome).[34]

When an adequate sample is obtained, endometrial biopsy has a high diagnostic accuracy for endometrial cancer,[35,36] although detection rates are lower in premenopausal women than in postmenopausal women.[36] The use of hormonal contraception (e.g. the progestogen-only injectable, which induces endometrial atrophy) may make obtaining an adequate endometrial sample difficult.[37]

Further investigation may be required if an adequate sample cannot be obtained and/or a woman's bleeding problems do not respond to treatment or resolve on stopping hormonal contraception.

5.6.2 Pelvic ultrasound scan and hysteroscopy

There is no guidance available for health professionals on the role of pelvic ultrasound scan and hysteroscopy in women using hormonal contraception who present with problematic bleeding.

In premenopausal women pelvic ultrasound scan alone is insufficient to exclude endometrial cancer. One-off assessment of endometrial thickness is of limited value in premenopausal women but may identify structural abnormalities, such as endometrial polyps or submucosal fibroids, which might be contributing to bleeding issues.[32,38] A pelvic ultrasound may also identify an IUS which is located low in the cavity, which limited evidence has suggested results in less uniform endometrial suppression and more days of bleeding and spotting when compared to fundally placed devices.[39]

A NICE guideline recommends that assessment of the uterine cavity via transvaginal ultrasound scan or hysteroscopy may be indicated in women with HMB if they also have signs or symptoms, such as intermenstrual or postcoital bleeding, pelvic pain or pelvic mass, suggestive of a structural abnormality.[32] There is no direct evidence that structural abnormalities (e.g. endometrial polyps or intrauterine fibroids) are a cause of problematic bleeding in women using hormonal contraception. If, however, these structural abnormalities are suspected, a transvaginal ultrasound scan and/or hysteroscopy may be considered.

✓ An endometrial biopsy should be considered in women aged ≥45 years or in women aged <45 years with risk factors for endometrial cancer who have persistent problematic bleeding after the first 3 months of use of a method or who present with a change in bleeding pattern.

✓ The role of endometrial polyps, fibroids or ovarian cysts as a cause of problematic bleeding is uncertain. Nevertheless, for all women using hormonal contraception with problematic bleeding, if such a structural abnormality is suspected a transvaginal ultrasound scan and/or hysteroscopy may be indicated.

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6 Treatment Options

Although numerous research studies have attempted to investigate preventative and therapeutic treatments for women using hormonal contraception who have problematic bleeding, few are of sufficient quality to guide management in clinical practice usefully.[40] As a consequence of this lack of evidence, Good Practice Points based on the opinion of the multidisciplinary group have been provided in this section unless otherwise stated.

The World Health Organization *Selected Practice Recommendations for Contraceptive Use* (WHOSPR)[15] provides recommendations on the management of bleeding abnormalities in women using progestogen-only implants, progestogen-only injectable and the LNG-IUS. Bleeding with hormonal contraceptives is common in the first 3 months of use. However, if requested by women, the limited therapeutic options available can be considered during this time.

6.1 Combined hormonal contraception

Problematic bleeding is less common with combined (estrogen and progestogen) hormonal methods than with progestogen-only methods.[8] Any unscheduled bleeding with a COC usually settles with time and therefore changing the COC to another COC in the first 3 months is not generally recommended. Women should use a COC with the lowest dose of ethinylestradiol (EE) to provide good cycle control.[41] Cycle control may be better with COC containing 30–35 µg EE than 20 µg EE.[41,42]

Although individual studies have suggested that bleeding may be better with COC containing certain progestogens,[43–46] this is not evident in systematic reviews.[47]

Scheduled withdrawal bleeding is often shorter and/or lighter among users of estradiol COC when compared to EE COC.[11] It is not clear if this effect is due to the type of estrogen, the type of progestogen or the shortened hormone-free interval in estradiol COC regimens.

Using a COC with an extended cycle is safe and well tolerated and indeed the number of days of bleeding is reduced.[11,48–59] However, there are currently no good data to support use of a continuous regimen over the licensed cyclical regimes to improve unscheduled bleeding.

A Cochrane Review has concluded that there is insufficient evidence to recommend the use of a biphasic or triphasic COC to improve bleeding patterns.[45,60]

Unscheduled bleeding with the contraceptive patch appeared similar to that for a triphasic COC in a randomised controlled trial (RCT),[61] although unscheduled bleeding was more common in Cycles 1 and 2 with patch use compared to COC use. A systematic review[9] reported that there was no significant difference in unscheduled bleeding between users of the contraceptive patch and COC users in three of the included studies; however, a fourth study reported less breakthrough bleeding in patch users.[9]

Cycle control may be better with the CVR than with COC.[9] This has also been demonstrated with extended regimens.[48,51]

✓ It is not generally recommended that a COC be changed within the first 3 months of use as bleeding disturbances often settle in this time.

✓ For women using a COC the lowest dose of EE to provide good cycle control should be used. However, the dose of EE can be increased to a maximum of 35 µg to provide good cycle control.

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6.2 Progestogen-only contraception

A Cochrane Review investigated preventive and therapeutic treatments of bleeding associated with progestogen-only contraception.[40] No evidence was identified to suggest that bleeding patterns with one progestogen-only method will predict the likely bleeding patterns with another progestogen-only method.

6.2.1 *Progestogen-only pills*

There is a lack of evidence on the effective treatment of bleeding in women using POP. Women may experience different bleeding patterns with the traditional POP and the DSG POP and could try switching to the other if bleeding is problematic. As a guide, women considering DSG-only contraception can be advised that after 12 months of use, over a 3-month period, approximately:

- 5 in 10 women can expect to be amenorrhoeic or have infrequent bleeding
- 4 in 10 women can expect to have 3–5 bleeding spotting/episodes (regular)
- 1 in 10 women can expect ≥6 bleeding/spotting episodes (frequent bleeding)
- In addition, 2 in 10 women will experience bleeding/spotting episodes lasting >14 days (prolonged bleeding).

Traditional POP users can be advised that frequent and irregular bleeding are common, while prolonged bleeding and amenorrhoea are less likely.[13,14]

Although bleeding may settle with time, there is no definite timeframe in which women can expect bleeding to stop or improve. There is no evidence that bleeding improves with taking two POP per day, although this has been used in clinical practice. Studies have investigated the use of an estrogen[62] or anti-progestogen[63] versus placebo for the treatment of bleeding associated with POP use with little effect.

6.2.2 *Progestogen-only injectable contraception*

Available evidence has reported that bleeding patterns are comparable for intramuscular and subcutaneous administration of depot medroxyprogesterone acetate (DMPA).[19]

One randomised trial[64] involving 278 DMPA users with irregular bleeding evaluated the effect of EE (50 µg), estrogen sulphate (2.5 mg) and placebo daily for 14 days on bleeding. Although this trial was designed to identify both short- and long-term effects, there was a high rate of discontinuation (40% in each group) and thus a major risk of bias. Only EE was effective in stopping bleeding in the 14 days of treatment [relative risk (RR) 0.26; 95% confidence interval (CI) 0.11–0.60]. In the 3 months following treatment, however, any ongoing beneficial effect on bleeding was minimal.

Low-dose (<50 µg) COC has not been proven to be effective in treating problematic bleeding in women using progestogen-only injectable contraception. However, an RCT[65] reported that the use of an estradiol vaginal ring during initiation of the progestogen-only injectable was well tolerated by participants and decreased total bleeding.

An RCT of use of the anti-progestogen mifepristone (50 mg as a single dose on Day 14 and every 2 weeks for six cycles) reported a significant reduction in breakthrough bleeding compared to women given placebo;[66] however, it is unclear whether mifepristone might reduce contraceptive efficacy.

The WHOSPR did not give any recommendation regarding the use of a non-steroidal anti-inflammatory drug (NSAID).[15] However, one trial has investigated the use of the NSAID mefenamic acid for women using DMPA.[67] Women had to have at least 8 days bleeding or spotting prior to participating in the trial and to be bleeding on the day of recruitment. This small,

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randomised, double-blind, placebo-controlled trial found that mefenamic acid (500 mg twice daily for 5 days) was effective in reducing a bleeding episode.[67] Around 70% of women had stopped bleeding within 7 days of starting mefenamic acid compared to 40% with placebo ($p<0.05$). There was no significant difference in the mean bleed-free interval in the longer term (28 days following treatment).

Tranexamic acid (250 mg four times daily for 5 days) has also been reported to be effective for reducing bleeding episodes in the short-term for users of DMPA but there are no data to demonstrate a prolonged effect.[68]

Despite the lack of evidence, the CEU would support the use of COC as a first-line option in women using progestogen-only injectable contraception who have problematic bleeding if there are no contraindications to use of estrogen. COC can be used for 3 months while continuing with DMPA. COC can be taken in the usual cyclical manner (with a withdrawal bleed) or continuously without a pill-free interval. This is an unlicensed use of COC and any risks associated with this dual administration are unknown.

Where there is a contraindication to COC use, mefenamic acid (500 mg twice or three times daily for 5 days) may be considered to attenuate a bleeding episode. There is no evidence that this approach has an effect on bleeding patterns in the longer-term. Tranexamic acid 1 g four times daily is an alternative.

6.2.3 *Progestogen-only implants*

Evidence relating to management of bleeding problems associated specifically with the etonogestrel implant is lacking. Data from studies in women using LNG implants (Norplant®) provide some evidence of a beneficial effect of mefenamic acid or EE (alone or as an oral contraceptive) on bleeding patterns.[69–72] To date there are no data to indicate whether or not this can be extrapolated to the etonogestrel implant.

Estrogen generally has been reported to have a beneficial effect in stopping bleeding in women using Norplant and may reduce irregular bleeding during treatment. In one study, a combination of oral EE (50 µg) with LNG (250 µg) taken for 20 consecutive days in Norplant users reduced bleeding during treatment and up to 8 weeks after treatment when compared to placebo.[72] This combined approach significantly reduced continued irregular bleeding during treatment compared to placebo (RR 0.08; 95% CI 0.03–0.24) and reduced unacceptable bleeding (as defined by the number of women having bleed-free intervals of <11 days) after treatment (RR 0.02; 95% CI 0.00–0.29).

There is limited evidence that LNG (0.03 mg) given alone twice daily for 20 days from the eighth consecutive day of bleeding reduced the number of days of bleeding over the following year of Norplant use.[70]

Research has suggested that mifepristone may be of some benefit in stopping bleeding episodes. Its use in this situation is not part of routine clinical practice and it could potentially impact on the contraceptive effectiveness of the progestogen-only implant.[73–76] Use of doxycycline to reduce bleeding has also been suggested, but evidence from studies does not support this.[76]

For women with either light or heavy bleeding with a progestogen-only implant, the use of estrogen in the form of COC or of an NSAID is recommended in the WHOSPR[15] and would be supported by the CEU (in the absence of contraindications). COC may be used for 3 months either in the usual cyclical manner or continuously without a pill-free interval. Such use is outside the product licence. Extended dual use of the COC and progestogen-only implant has not been studied and therefore any risks associated with this practice are unknown. The decision to co-administer the COC and progestogen-only implant beyond 3 months is a matter of individual clinical judgement.[21]

6.2.4 *Levonorgestrel-releasing intrauterine system*

Bleeding is very common in the first 3 months of LNG-IUS use. It may be prolonged and may take 6 months or longer to settle. Therefore, good provision of information about expected bleeding patterns likely to be experienced is an important part of management.

A limited volume of evidence was identified which examined treatment options for women with bleeding with the 52 mg LNG-IUS. A small RCT[77] randomised 129 IUS users to naproxen, estradiol and placebo treatment arms. When compared to placebo the naproxen cohort was more likely to be in the lowest quartile of bleeding and spotting. Multivariate analysis suggested that the naproxen group had a 10% reduction in bleeding and spotting days (adjusted RR 0.90, 95% CI 0.84–0.97) when compared to placebo. More frequent bleeding and spotting were observed in the estradiol group (adjusted RR 1.25, 95% CI 1.17–1.34).[77]

Another small RCT,[78] with 204 participants, reported that tranexamic acid (500 mg) and mefenamic acid (500 mg) three times daily over a 90-day treatment period were ineffective and did not alleviate bleeding or spotting. An RCT,[79] with 136 participants, reported that ulipristal acetate, the selective progesterone receptor modulator, 150 mg in divided doses at Days 21, 49 and 77 following 52 mg LNG-IUS insertion, was effective initially as a treatment for bleeding and spotting but that the effectiveness did not persist in the long term.

In the absence of evidence, the FSRH guidance on *Intrauterine Contraception* (2015) suggests that COC could be used for 3 months for problematic bleeding with the IUS if a woman has no contraindications.[24]

✓ Bleeding is common in the initial months of progestogen-only method use and may settle without treatment. If treatment encourages a woman to continue with the method it may be considered.

✓ There is no evidence that changing the type and dose of POP will improve problematic bleeding; bleeding patterns may vary with different POP preparations and this may help some individuals.

B For women using a progestogen-only injectable contraceptive who have problematic bleeding, mefenamic acid 500 mg twice daily (or as licensed up to three times daily) for 5 days can reduce the length of a bleeding episode but has little effect on bleeding in the longer term.

C For women with problematic bleeding using a progestogen-only injectable, implant or IUS who wish to continue with the method and are medically eligible, a COC may be tried for 3 months (this can be used in the usual cyclic manner or continuously without a pill-free interval and is outside the product licence).

✓ Longer-term use of COC has not been studied in relation to the progestogen-only injectable, implant or IUS methods. If bleeding recurs following 3 months use of COC, longer-term use is a matter of clinical judgement.

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APPENDIX 1: DEVELOPMENT OF CEU GUIDANCE

GUIDELINE DEVELOPMENT GROUP

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Declared Interests

Dr Sharon Cameron has received research funding from HRA Pharma (France) and Sayana (USA), has given lectures on behalf of HRA Pharma (France) and is a scientific advisor to Sayana (UK) and Exelgyn (France).

Dr Karin Piegsa has received lecture fees for delivering non-promotional update sessions to general practice. Her department has received payment from Bayer and Merck, Sharp and Dohme towards training fees for subdermal implant training.

Professor Edith Weisberg has provided expert opinion for MSD and Bayer Healthcare, has been supported to attend conferences by Bayer Healthcare and has obtained research funding for investigator-initiated research from both companies.

Administrative support to the CEU team was provided by **Mr John Matthews**.

Patient Consultation

A questionnaire on the proposed guidance content was completed by a sample of potential users.

Clinical Effectiveness Unit (CEU) guidance is developed in collaboration with the Clinical Effectiveness Committee (CEC) of the FSRH. The CEU guidance development process employs standard methodology and makes use of systematic literature review and a multidisciplinary group of professionals. The multidisciplinary group is identified by the CEU for their expertise in the topic area and typically includes clinicians working in family planning, sexual and reproductive health care, general practice, other allied specialities, and user representation. In addition, the aim is to include a representative from the FSRH CEC, the FSRH Meetings Committee and FSRH Council in the multidisciplinary group.

Evidence is identified using a systematic literature review and electronic searches are performed for: MEDLINE (1996–2015); EMBASE (1996–2015); PubMed (1996–2015); The Cochrane Library (to 2015) and the US National Guideline Clearing House. The searches are performed using relevant medical subject headings (MeSH), terms and text words. The Cochrane Library is searched for relevant systematic reviews, meta-analyses and controlled trials relevant to unscheduled bleeding. Previously existing guidelines from the FSRH (formerly the Faculty of Family Planning and Reproductive Health Care), the Royal College of Obstetricians and Gynaecologists (RCOG), the World Health Organization (WHO) and the British Association for Sexual Health and HIV (BASHH), and reference lists of identified publications, are also searched. Summary evidence tables are available on request from the CEU. The process for development of CEU guidance is detailed on the FSRH website (www.fsrh.org). The methods used in development of this guidance (CEU Process Manual version 4.0) have been accredited by NHS Evidence.

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Questions for Continuing Professional Development

The following questions have been developed for continuing professional development (CPD) based on this guidance document.

The answers to the questions and information on claiming CPD points can be found in the 'members-only section' of the FSRH website (www.fsrh.org), which is accessible to all Diplomates, Members, Associate Members and Fellows of the FSRH.

1 **All sexually active women presenting with problematic bleeding when using hormonal contraceptives should be:**

a. Assessed for sexually transmitted infections (STIs)
b. Given a speculum and bimanual examination
c. Advised to change their method
d. Offered cervical screening

2 **A 25-year-old woman presents, 2 months after starting her 20 µg combined oral contraceptive pill (COC), complaining of spotting. She wants to know if she should try another method. She has no change in sexual history. What is the most single most appropriate management in the first instance?**

a. Advise she continue with her current pill as it will settle down
b. Advise that 50% of users experience irregular bleeding and suggest stopping
c. Suggest waiting a further month and then consider a 30 µg COC
d. Switch her to another 20 µg COC with a different progestogen immediately

3 **A 25-year-old woman who has been using the progestogen-only implant presents complaining of irregular bleeding since starting 7 months ago and would like treatment or for it to be removed. She has no significant medical history. After consideration and exclusion of other factors, what is the single most appropriate treatment to offer her?**

a. COC
b. Doxycline
c. Mefenamic acid
d. Mifepristone and ethinylestradiol

4 **A 25-year-old woman who has been using the progestogen-only injectable presents complaining of frequent bleeding since her second injection 6 weeks ago. She experiences migraine with aura. After consideration and exclusion of other factors, what is the single most appropriate treatment to offer her in the first instance?**

a. A COC used cyclically or continuously for 3 months
b. Another injection of depot medroxyprogesterone acetate
c. Mefenamic acid
d. The desogestrel (DSG) progestogen-only pill (POP) once daily

5 **A 34-year-old woman who has been using the POP presents complaining of erratic bleeding. She has been using her levonorgestrel (LNG) pill for 4 months. She is not happy and wants to know if there is any solution. She has already tried a norethisterone pill. After consideration and exclusion of other factors, what is the single most appropriate advice to offer her?**

a. Advise she can try the DSG POP to see if the pattern is more acceptable
b. Advise that her bleeding will settle by 6 months of use
c. Advise that her bleeding pattern is likely to be like this with all progestogen-only methods
d. Use a COC in addition to the POP for 3 months

6 **A 51-year-old woman who has been using the POP for the past 10 years with regular bleeds presents complaining that these are becoming erratic and more frequent. She has had no change in partner and has not missed any pills. What is the single most appropriate management of this woman?**

a. Advise she is likely menopausal and that contraception can be stopped
b. Advise she should take two POP a day to regulate her bleeding
c. Examine the patient and exclude pregnancy and pathology before changing her contraception
d. Switch her onto a combined hormonal contraceptive to regulate her bleeding

7 **An 18-year-old woman presents complaining of irregular bleeding with the progestogen-only implant. She has had the implant for 8 months. She indicates that her bleeding has become frequent in the last 6 weeks. She has a new partner of 2 months and takes no additional medication. What is the single most appropriate test to offer this woman in the first instance?**

a. Cervical screening
b. Urine test for STIs
c. Pregnancy test
d. Self-taken lower vaginal swab

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8 **A 26-year-old woman presents with persistent bleeding since starting the progestogen-only implant 4 months ago. She is up to date with cervical screening and has not been sexually active in the last 4 weeks because of the bleeding and associated pelvic pain. What is the most appropriate course of action in the first instance?**

a. Advise bleeding can remain irregular and suggest changing method
b. Advise bleeding usually settles with time, offer COC
c. Advise needs a speculum and bimanual examination
d. Advise needs a speculum examination

9 **A 37-year-old woman who has had the levonorgestrel-releasing intrauterine system (LNG-IUS) for 9 months complains about the irregular spotting she has always experienced with this method. She wishes to control the bleeding while on holiday. She has no contraindications to hormonal contraceptives. What is the single most appropriate treatment to offer in the first instance to control her bleeding pattern?**

a. A 20 µg COC
b. A 30–35 µg COC
c. A DSG POP
d. A LNG POP

10 **A 40-year-old woman presents complaining about her bleeding patterns since having the LNG-IUS inserted 4 months ago. She says she was misled and that she had been told she would have no bleeding. What is the single most appropriate advice to give her regarding bleeding patterns associated with the LNG-IUS?**

a. Irregular, light or heavy bleeding is common in the first 6 months. By 3 years, one quarter of women will have no bleeding
b. Irregular, light or heavy bleeding is common in the first 6 months. Thereafter women have regular monthly bleeds
c. Most women have no bleeding after 3 months of use. However, a small number of women will continue to bleed until 6 months
d. Most women have no bleeding after 6 months of use. However, a small number of women will continue to bleed until 12 months

What learning needs did this guidance address and how will it change your practice? (Please write below)

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Auditable Outcomes for Problematic Bleeding with Hormonal Contraception

The following auditable outcomes have been suggested by the FSRH Clinical Standards Committee

Auditable Outcomes

1 Percentage of women who have a documented discussion on possible bleeding patterns that may occur at the time of commencing hormonal contraception. [Audit standard 97%]

2 Percentage of women with a change in bleeding pattern or problematic bleeding for >3/12 months who have a clinical history documented highlighting possible causes of problematic bleeding. [Audit standard 97%]

3 Percentage of women with a change in bleeding pattern or problematic bleeding for >3/12 months who have had a speculum examination with bimanual examination performed and documented if additional symptoms have occurred (i.e. pelvic pain, intermenstrual bleeding, postcoital bleeding). [Audit standard 97%]

4 Percentage of women with a change in bleeding pattern or >3/12 months of problematic bleeding who are aged <25 years or >25 years with risk factors for sexual infections and have had a sexual history clearly documented and chlamydia and gonorrhoea tests performed. [Auditable standard 97%]

5 Percentage of women aged >25 years (Scotland >20 years) who have a documented discussion of their participation in a National Health Service Cervical Screening Programme and date of when their last smear test was taken. [Auditable standard 97%]

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COMMENTS AND FEEDBACK ON PUBLISHED GUIDANCE

All comments on published guidance can be sent directly to the Faculty of Sexual & Reproductive Healthcare (FSRH) at **mail@fsrh.org.**

The FSRH is unable to respond individually to all feedback. However, the FSRH will review all comments and provide an anonymised summary of comments and responses, which are reviewed by the Clinical Effectiveness Committee and any necessary amendments made.